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INVITED EDITORIAL

Prostate Cancer

The metastatic castration-resistant prostate cancer treatment paradigm: more choices, more questions

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The world of prostate cancer has dramatically changed in the last few years. The original paradigm that metastatic castration-resistant prostate cancer (mCRPC) is untreatable is clearly wrong.

In 2004, docetaxel demonstrated a modest, yet meaningful survival and pain palliative benefit.[1,2] The field then went through a long approval "drought," where a number of drug combinations with docetaxel were not found to add benefit;[3–7] no new therapeutic agents were approved again until 2010. Since then, however, we have seen the approval of sipuleucel-T,[8] cabazitaxel,[9] abiraterone,[10,11] enzalutamide[12] and radium-223[13] broaden the menu of agents that prolong overall survival in mCRPC. In addition, denosumab was found to be superior in time to the skeletal-related event (SRE) over zoledronic acid for those with castration-resistant bone metastases.[14]

What is most remarkable is that each new agent listed above has a distinct mechanism of action. Although each is moderately effective, none of these agents offer a cure and the biologic and clinical data to explain mechanisms of drug resistance remains scanty at best. As a result, the field must now rely on practical considerations, with much data extrapolation, to fuel logical utilization and sequencing of these therapies in hopes of achieving optimal patient outcomes.

In this special issue, these new agents will be discussed thoroughly. This includes review of biologic mechanism of action, clinical efficacy and safety data, biomarkers and opinions on pragmatic use and combinations for future exploration. Although, the topics may be drug-focused, there is the inclusion of broad discussion on entire fields of therapy with historical and pre-clinical perspective. This includes a review of traditional chemotherapy, immunotherapy, hormonal agents, bone-specific therapy and other pathways currently under exploration with therapeutic agents in clinical testing.

Although, these articles are extremely comprehensive in nature, we must recognize that more therapeutic options naturally lead to more questions of how best to optimize treatment outcomes. Below, we propose some of the most pressing questions facing clinicians in the field of mCRPC. This discussion is accompanied with the caveat that our successes have led to more questions than answers.

WHEN SHOULD SIPULEUCEL-T BE ADMINISTERED?

Sipuleucel-T administration comes with many challenges such as lack of prostate-specific antigen (PSA) decline, lack of improvement in progression endpoints and no clear predictive or response biomarkers. Singh and Gulley[15] discuss data from the IMPACT trial that shows that those with the lowest PSA quartile levels at baseline derive the greatest benefit from sipuleucel-T compared to placebo.[16] Although retrospective, these data support the concept that earlier introduction of immunotherapy in patients with a lower disease burden may be optimal. The authors also discuss emerging blood- and tissue-based immune markers that offer pharmacodynamic evidence of *in vivo* immune response, many with survival correlates.[17] With increasing evidence supporting the use of immunotherapy in cancers in general and specifically in prostate cancer, it is important to recognize the difference in antineoplastic kinetics,[18] shed traditional methods of measuring antitumor treatment response and instead, seek new endpoints that capture meaningful clinical benefit. This will require persistent focus on discovery of predictive biomarkers that can be readily accessible in clinic.

ABIRATERONE, ENZALUTAMIDE AND BEYOND. HOW SHOULD WE BE SEQUENCING NEW ANDROGEN SIGNALING INHIBITORS?

Potent agents that target the androgen/androgen receptor (AR) axis are being utilized earlier in the mCRPC treatment paradigm. Stein[19] provides a refined discussion on abiraterone and other androgen synthesis inhibitors. With the recent PREVAIL data,[20] enzalutamide will likely receive regulatory approval in the pre-chemotherapy space in the near future. Yet, there is scant data surrounding sequencing of abiraterone and enzalutamide. Multiple retrospective reports describe the blunted response to the second of these two agents when given in sequence.[21–28] Yet, a substantial proportion of patients still respond to the second agent, emphasizing a biologic principal that mechanisms of resistance to androgen synthesis inhibitors and potent AR inhibitors may be distinct in a subset of patients. For the time being, practical factors such as patient comorbidities and issues surrounding steroid use may determine selection and sequencing of abiraterone and enzalutamide.[29] Identifying mechanisms of resistance to these agents should help us to optimize sequencing of drugs and allow biologically rational combinations to be tested.

WHEN IS THE OPTIMAL TIMING FOR CHEMOTHERAPY?

With the introduction of potent novel hormonal therapies with favorable toxicity

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profiles, it is not surprising that traditional chemotherapy is being pushed further back in the treatment paradigm. However, there are ongoing trials studying optimal use of docetaxel, cabazitaxel and novel combinations.[30] In addition, we eagerly await the upcoming presentation of data from ECOG 3805 which has described in the press release format that adding 6 cycles of docetaxel chemotherapy to standard androgen deprivation therapy (ADT) at the time of new metastatic prostate cancer offers a significant survival advantage (http://www.nih.gov/news/health/dec2013/nci-05.htm). There will be much to consider and scrutinize, including side-effect profiles, quality of life measures and degree of efficacy. Overall, this prompts the question: when is the best time to initiate chemotherapy? Will positive survival data from a hormone-sensitive trial lead clinicians to introduce chemotherapy at the earliest point possible or will chemotherapeutic agents continue to be pushed later due to issues of tolerability and quality of life?

RADIUM-223 OFFERS SURVIVAL BENEFIT IN BONE MCRPC, BOTH IN THE PRE- AND POST-CHEMOTHERAPY SETTING. WHEN SHOULD WE USE IT?

Radium-223 is the newest agent to be added to the mCRPC treatment menu, as it was recently approved for patients with symptomatic bone metastasis who lack visceral metastasis. This alpha-emitting radiopharmaceutical is attractive since it seems to carry low toxicity while offering overall survival, symptomatic skeletal event (SSE) and pain palliative benefits.[31] Yet there are many unanswered questions still in the early days of this agent. For instance, why does PSA inconsistently correlate with outcomes? What should we expect with imaging in patients undergoing radium-223 and can it help us tailor therapy?

However, the most practical issue for clinicians is whether there is an optimal sequence to use radium-223 with other agents, including chemotherapy? Patients who have received prior chemotherapy or radiation and those with more bone metastases are at greatest risk of myelosuppression after administration of radium-223.[32] Therefore, patients that have been more heavily pre-treated may be more limited in ability to receive and complete the full 6 cycles of radium-223. Meanwhile, there are fewer restrictions and greater flexibility for clinicians to decide on chemotherapy usage and dosing. This leads to the question of whether radium-223 is best administered early?

ARE BONE-TARGETED THERAPIES STILL AS IMPORTANT IN THIS DISEASE AS THEY ONCE WERE?

Bone morbidity remains a major complication that all patients face and utilization of bone-targeted therapy with either denosumab or zoledronic acid effectively decrease skeletal events.[14,33] However, special attention needs to be paid to this topic in prostate cancer. One important point is that all the positive skeletal event prevention trials were performed in patients with castration-resistant disease.[34] In the metastatic hormone-sensitive setting, early introduction of zoledronic acid did not offer a SRE benefit.[35] A natural extrapolation is that ADT is highly efficacious and patients undergoing effective therapy are likely have less skeletal morbidity, perhaps negating the need for bone supportive therapy. In the modern era, highly efficacious agents such as abiraterone, enzalutamide and radium-223 have all demonstrated survival and SRE benefit.[12,13,36] Therefore, we are left with practical considerations as to whether anti SRE-only therapy should continue to be extensively utilized or reserved for special situations.

WHAT NEW TARGETS AND PATHWAYS ARE BEING ADDRESSED IN ONGOING AND FUTURE CLINICAL TRIALS?

This is the broadest question, so we have selected a few promising targets and pathways for this special issue. The PI3K-AKT-mTOR axis is important in many cancers but has gained much attention in prostate cancer recently.[37] The concept of reciprocal activation between the PI3K-AKT-mTOR and AR signaling pathways have led to enthusiasm to combine inhibitors of this pathway with novel AR axis drugs.[38] Similarly, Zhang discusses rationale for poly (ADP-ribose) polymerase inhibition in combination with ADT, chemotherapy and radiation therapy in prostate cancer.[39] Inhibiting clusterin, an anti-apoptotic protein through direct inhibition of Bax activation,[40] may help alleviate docetaxel resistance; the field eagerly awaits phase 3 results of a randomized, phase 3 combination trial of docetaxel with custirsen, an antisense to clusterin.[41] Bilusic and Wong review the "lessons learned" from failed anti-angiogenic agents in prostate cancer such as bevacizumab, sorafenib, sunitinib, aflibercept, thalidomide and lenolidamide.[42] Importantly, the endpoints utilized in most of those trials may not have been ideal to capture efficacy of an anti-angiogenic agent against prostate cancer. However, we still await the results from phase 3 trials with cabozantinib and tasquinimod in mCRPC.

In summary, the therapeutic advancements for mCRPC have created multiple new challenges moving forward. The most obvious change is that placebo-controlled trials to demonstrate overall survival will likely not happen moving forward. Thus, the regulatory options for developing a new drug will either be in combination with an existing agent, for an indication created with a new disease state, or perhaps direct comparison with one of the new highly efficacious agents. Another consideration is to move earlier and an example of this is with ARN-509, a pure AR antagonist being tested in the SPARTAN trial (NCT01946204) in the M0 CRPC, or non-mCRPC, disease state. The obvious challenge with moving earlier is finding a meaningful endpoint that not only has clinical impact but also meets regulatory hurdles. Otherwise, enormous trials with extremely long follow-up would test the field in terms of the patient and financial resources. Regardless, greater efforts must be made to understand tumor biology and mechanisms of drug sensitivity and resistance. We challenge the field to develop predictive and response biomarkers while maturing efforts to biologically characterize individual patient tumors through circulating tumor cells, metastatic biopsies, imaging and other creative means.

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